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Review Article

The use of misoprostol in termination of second-trimester pregnancy

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Abstract

Misoprostol, a synthetic prostaglandin E1 analog, is initially used to prevent peptic ulcer. The initial US Food and Drug Administration-approved indication in the product labeling is the treatment and prevention of intestinal ulcer disease resulting from nonsteroidal anti-inflammatory drugs use. In recent two decades, misoprostol has approved to be an effective agent for termination of pregnancy in various gestation, cervical ripening, labor induction in term pregnancy, and possible management of postpartum hemorrhage. For the termination of second-trimester pregnancy using the combination of mifepristone and misoprostol seems to have the highest efficacy and the shortest time interval of abortion. When mifepristone is not available, misoprostol alone is a good alternative. Misoprostol, 400 μg given vaginally every 3–6 hours, is probably the optimal regimen for second-trimester abortion. More than 800 μg of misoprostol is likely to have more side effects, especially diarrhea. Although misoprostol can be used in women with scarred uterus for termination of second-trimester pregnancy, it is recommended that women with a scarred uterus should receive lower doses and do not double the dose if there is no initial response. It is also important for us to recognize the associated teratogenic effects of misoprostol and thorough consultation before prescribing this medication to patients regarding these risks, especially when failure of abortion occurs, is needed.

Keywords: Misoprostol; PGE1; Pregnancy; Second trimester; Termination

Introduction

Misoprostol, a synthetic prostaglandin E1 (PGE1) analog, is initially used to prevent peptic ulcer. The initial Food and Drug Administration (FDA)-approved indication in the product label is the treatment and prevention of intestinal ulcer disease resulting from nonsteroidal anti-inflammatory drugs (NSAIDs) use. However, because of its cervical ripening and uterotonic properties, misoprostol has begun to be abused for illegal abortion since late 1980s. After serial trials in recent two decades, misoprostol became one of the most useful drugs in termination of pregnancy and also for induction of labor.

In this review article, we will talk about the development of misoprostol and the use of misoprostol in termination of second-trimester pregnancy.

The pharmacologic properties of misoprostol

Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl analog of PGE1 and is water soluble. The most common commercial preparation available in Taiwan is Cytotec (Pfizer, New York, NY, USA) tablets (200 μg) that contains the

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inactive ingredients hydrogenated castor oil, hydroxypropyl methylcellulose, microcrystalline cellulose, and sodium starch glycolate [1]. The bioactivity of misoprostol is characterized by rapid absorption, extensive metabolism, and rapid excretion. After oral administration, the T_{max} of misoprostol acid is 12 ± 3 minutes with a terminal half-life of 20–40 minutes [2]. There is high variability of plasma levels of misoprostol acid after single doses showing a linear relationship with dose over the range of 200–400 μg. No accumulation of misoprostol acid was noted in multiple dose studies and a plasma steady state was achieved within 2 days. Misoprostol is mainly metabolized in the liver, and less than 1% excreted in the urine [3]. There is no known drug interaction of misoprostol.

In the beginning, misoprostol was only used as an oral tablet, but many studies showed many different routes of administration, such as vaginal route, sublingual route, and buccal route [4]. Some pharmacokinetic studies show the systemic bioavailability with vaginal route is three times higher than that of oral route. Another study from Lumbiganon et al [5] concluded that sublingual misoprostol reached peak concentration in the shortest time and had the highest bioavailability comparison with vaginal and oral routes.

The development of misoprostol

In 1982, misoprostol was confirmed to have antisecretory activity and mucosal protective effect on the gastrointestinal mucosa of human beings [6]. It became the first medication used in a multicenter, randomized, double-blind trial for patients with peptic ulcer disease since 1985 [7]. Since then, misoprostol was widely marketed for the prevention and treatment of peptic ulcer disease [8]. The oral tablet of misoprostol was approved by the FDA in 1988 for the prevention and treatment of gastric ulcers associated with the use of NSAIDs.

However, misoprostol became a widely used abortifacient after its introduction since 1986, especially by women in countries where abortion was illegal or limited in special conditions [2]. In 1987, the first report of the potential effect of misoprostol for the termination of pregnancy was published [9], partial or complete abortion, vaginal bleeding, and softening of the cervix were all significantly increased after the use of misoprostol. Another report about the abuse of misoprostol for illegal abortion was published in 1991 [10]. In fact, most of these publications came from Brazil and other countries in South and Central America. Lower cost, convenience of use, and less traumatic than other abortion methods were the reasons of abuse. Thereafter, several trials about misoprostol for termination of pregnancy were reported and showed a strong evidence for the efficacy and relative safety in obstetrical and gynecological practice.

In fact, misoprostol had drawn out a debate in the literature from the antiabortion lobby, the manufacturer (Searle), American College of Obstetricians and Gynecologists, and a lots of conflict and fight occurred between them. After some issues, on April 17, 2002, the FDA finally approved a new label for the use of misoprostol during pregnancy [11]. The new label of use for misoprostol suggests that the contraindication is only for pregnant women who are using the medication to reduce the risk of NSAID-induced gastric ulcers. Since then, misoprostol becomes a legitimate part of the FDA-approved regimen for use with mifepristone to induce abortion in early pregnancy and is also recognized for its use for induction of labor [2]. And the World Health Organization also recommended the use of misoprostol in termination of pregnancy in various gestations [12]. In recent two decades, misoprostol has approved not only to be an effective agent for termination of pregnancy in various gestation and also useful in cervical ripening, labor induction in term pregnancy, treatment of incomplete abortion [13], and possible management of postpartum hemorrhage [14].

Termination of pregnancy with misoprostol

Of the various PG analogs, misoprostol is the drug of choice as it is cheap, stable at room temperature, and available in most countries. It has been used orally, vaginally, or sublingually for medical abortion.

In the 1970s, several PGs have been shown to have abortifacient, which is effective for inducing abortion [15]. By the 1980s, more analogs of PG were reported to be effective for abortion, such as parenteral sulprostone and intravaginal gemeprost. However, the adverse side effects of these medications and the higher cost made them unsuitable as single agents for abortion. In 1987, the first report of the potential effect of misoprostol for the termination of the first-trimester pregnancy was published [16]. In 1991, Norman et al [17] reported the effect of misoprostol on uterine contractility and showed that misoprostol, with or without mifepristone, resulted in augmentation of the amplitude and frequency of uterine contractions. This publication was a landmark study of misoprostol and let it be a promising uterotonic agent. After this report, many researchers became interested in the effect of misoprostol as a cervical priming agent before surgical abortion or medical abortion.

Termination of second-trimester pregnancy

The ability of early prenatal diagnosis of fetal anomalies has expanded the indications for termination of pregnancy in the second trimester [18]. A variety of methods such as dilation and evacuation (D&E), systemic medications, intra-amniotic or extra-amniotic abortifacients, and hysterotomy have been used [19]. The traditional use of D&E in the second trimester basically is safe and effective. However, its safety depends on the surgeon's skill and experience, and it may cause psychologically trauma. Thus, less traumatic and noninvasive methods for termination of pregnancy seem to be the better choices. Furthermore, if the fetus can be delivered intact, it can give us more detailed information for further pathological and cytogenetic diagnosis. This information is very important for prenatal counseling in the future. Therefore, an alternative method is required to replace the use of D&E.

Many alternative methods for medical termination of second-trimester pregnancy are recommended, including intra-amniotic hypertonic saline or urea, intra-amniotic PGF2α infusion, oxytocin infusion, and vaginal gemeprost administration [20].

Leihair et al [21] first described the use of transvaginal misoprostol for expulsion of arrested gestational product in the second trimester in 1989. Since then, many studies have been reported. Baird et al [22] reported that misoprostol has effects on uterine tone similar to that of other PGs. Bugalho et al [23] and Yapar et al [24] published the further assessment of intravaginal administration of misoprostol. Fetal expulsion was successfully achieved in almost 90% of 132 cases who received 800–1600 μg misoprostol (800 μg dosage with successively reduced to 600 μg, 400 μg, and 200 μg). The mean abortion time was 14.3 hours. Elsheikh et al [25] concluded that the high efficacy and low incidence of side effects make misoprostol an useful alternative for second-trimester termination of pregnancy.

Misoprostol with mifepristone

There were some reports talk about the use of combination of mifepristone and misoprostol, which could possibly fasten the mean abortion time and improve the efficacy. Ashok and Templeton [26] reviewed 500 consecutive cases of medical abortion in second trimester of pregnancy and concluded that the combination of mifepristone followed by misoprostol provided a noninvasive and effective regimen for this indication. Another present study reported that combination of mifepristone followed by misoprostol could achieve a high successful rate (95.9%) of abortion within 24 hours and mean abortion time was 6 hours [27].

In Table 1 [26–33], we can see the results from those studies with the regimen of mifepristone and misoprostol. The mean abortion time after the use of misoprostol ranged from 5.4 hours to 10 hours. The conventional timing of misoprostol administration after mifepristone for second-trimester medical abortion is 36–48 hours. Li et al [34,35] had reported their simultaneous use of mifepristone and misoprostol for early pregnancy termination with a better result. However, Chai et al [36] published their report and supported that simultaneous use of mifepristone and misoprostol for second-trimester medical abortion is not as effective as the regimen using a 36–38-hour dosing interval.

Thus, the pretreatment with mifepristone (200 mg) 36–48 hours before administration of misoprostol is a good choice to terminate the mid-trimester pregnancy.

With misoprostol alone

When mifepristone is not available, misoprostol alone is also an efficient method. There were many different studies talking about this issue, including the variation in dosage, time interval, and the route of administration were well discussed.

Table 1
Misoprostol with mifepristone

Author	No. of individuals	Gestational age (wk)	Regimen with mifepristone	Misoprostol route	Misoprostol dose (μg)	Misoprostol time interval	Abortion rate within 24 h	Induction-abortion interval mean (h)
El-Refaey and Templeton [28]	70	13–20	600 mg 36–48 h prior	Vaginally	600	Followed by 400 μg q3 h × 5	97% (24–48 h)	6.0
			600 mg 36–48 h prior	Vaginally	600	Followed by 400 μg q3 h × 5 orally	97% (24–48 h)	6.7
Ashok and Templeton [26]	500	13–21	200 mg 36–48 h prior	Vaginally	800	Followed by 400 μg q3 h × 4 orally	97.2%	6.5
Ngai et al [29]	142	14–20	200 mg 36–48 h prior	Vaginally	200	q3 h × 5	84%	10.0
			200 mg 36–48 h prior	Orally	400	q3 h × 5	81.4%	10.4
Ashok et al [27]	1002	13–21	200 mg 36–48 h prior	Vaginally	800	Followed by 400 μg q3 h × 4 orally	97.1%	6.25
Tang et al [30]	120	12–20	200 mg 36–48 h prior	Sublingually	400	Placebo 2 tabs q3 h × 5 orally	91.4%	5.5
			200 mg 36–48 h prior	Orally	400	Placebo 2 tabs q3 h × 5 sublingually	85% (24–48 h)	7.5
Hamoda et al [31]	76	13–20	200 mg 36–48 h prior	Vaginally	800	Followed by 400 μg q3 h × 5	—	5.4
			200 mg 36–48 h prior	Sublingually	600	Followed by 400 μg q3 h × 5	—	5.27
Hou et al [32]	100	13–16	200 mg 1 d prior	Vaginally	600	Followed by 400 μg q6 h × 2 orally	94%	7.0
			200 mg 2 d prior	Vaginally	600	Followed by 400 μg q6 h × 2 orally	100%	6.8
Brouns et al [33]	176	16–24	200 mg 36–48 h prior	Vaginally	200	q4 h × 10	66%	11.6
			200 mg 36–48 h prior	Vaginally	400	q4 h × 4	73%	9.3

Compare with other methods

Some studies compare the efficacy with other modalities, such as intra-amniotic PGF2α infusion, oxytocin infusion, and vaginal gemeprost administration. Three randomized controlled trials compared vaginal misoprostol with gemeprost among women with live and dead fetuses in the second trimester. All of them found that misoprostol is as effective as, or more effective than, gemeprost. Jain et al [37] showed that intravaginal misoprostol administration is at least as effective as PGE2 gel for second-trimester pregnancy termination. In our report in 2000 [19], the comparison of intravaginal misoprostol administration (800 μg) with extra-amniotic foley traction using PGF2α infusion for termination of second-trimester pregnancy resulted in similar successful rates of 92.8% and 88.5%, respectively, and a shorter mean abortion time (10.4 ± 6.7 hours) for the misoprostol group. Another study by Ghorab and El Helw [38] compared endocervical misoprostol and extra-amniotic PGF2α and showed that misoprostol was more effective. Thus, it seems that the regimen of misoprostol alone is as effective or even more effective than other regimens.

About the dosage

The required amount of misoprostol not only decreases with increasing gestational age, but has also been found to be lower in women with a died fetus [4]. In 2002, Dickinson and Evans [39] introduced a randomized trial comparing three regimens of intravaginal misoprostol (200 μg hourly; 400 μg 6 hourly; 600 μg loading dose followed by 200 μg 6 hourly) suggested that the 400 μg regimen was preferred. Their latter publication of randomized controlled trial on a comparison of oral and vaginal misoprostol (400 μg orally 3 hourly; 400 μg vaginally 6 hourly; vaginally 600 μg loading dose then 200 μg orally 3 hourly) showed similar results. The oral regimens showed significant inferiority over the vaginal regimen in the abortion rate within 24 hours. The increased dosage was associated with a higher incidence of side effects [40]. Some authors recommended that more than 800 μg of misoprostol is likely to have more side effects, especially diarrhea [41,42]. The studies in Table 2 [42–52] showed that doses of 400 μg seem like an effective dosage with good efficacy.

About the interval of use

In the studies by Wong et al [44], they suggested that misoprostol could be administered at longer than 3-hour intervals to reduce its side effects, and the 3-hour regimen provides a significantly shorter abortion interval and higher percentage of successful abortion within 48 hours than the 6-hour interval group. The incidence of side effects was similar in the two groups excluding fever. Another pilot study from Taiwan showed that oral administration of 200 μg misoprostol at hourly intervals is also a promising method for termination of mid-trimester pregnancies, the means of induction to delivery interval was 12.0 hours with 81.3% women undergoing vaginal delivery within 24 hours, and the side effects was not significantly increased [52], but the case number is too small to have a new conclusion. The latest Cochrane Database reviewed four randomized controlled trials for termination of mid-trimester pregnancy (12–28 weeks'

Table 2
Misoprostol alone

Author	No. of individuals	Gestational age (wk)	Misoprostol route	Misoprostol dose (μg)	Misoprostol time interval	Abortion rate within 24 h	Induction-abortion interval mean (h)
Dickinson et al [43]	100	14–28	Vaginally (Group 2)	200	q6 h × 4	74.9%	16.9
Wong et al [44]	140	14–20	Vaginally (Group b)	400	q3 h × 5	73%	14.1
Jain et al [37]	100	12–22	Vaginally	200	q6 h × 48 h	80.9%	13.8
			Vaginally	200	q12 h × 48 h	86.5%	14.0
Wong et al [42]	148	14–20	Vaginally	400	q3 h × 5	80%	15.2
			Vaginally	400	q6 h × 3	60.8%	19
Bebbington et al [45]	114	Mid-trimester	Orally	200	q1 h × 3 followed by 400 μg q4 h × 6	38.5%	34.5
Dickinson and Evans [39]	150	14–30	Vaginally	200	q6 h × 48 h	58.8%	18.2
			Vaginally	400	q6 h × 48 h	76%	15.1
			Vaginally	600	Followed by 200 μg q6 h × 48 h	79.6%	13.2
Tang et al [46]	224	12–20	Sublingually	400	q3 h × 5	72%	12.2
			Vaginally	400	q3 h × 5	86%	10.5
Bhattacharjee et al [47]	300	13–20	Sublingually	400	q3 h × 8	79.8%	12
			Vaginally	400	q3 h × 8	85.9%	12.3
Carbonell et al [48]	210	12–20	Vaginally	600	q6 h × 4	98.1%	10.7
			Vaginally	400	q4 h × 5	94.3%	11.5
Caliskan et al [49]	162	15–22	Sublingually	100	q2 h	92.6%	7.4
			Sublingually	200	q2 h	91.4%	7.6
von Hertzen et al [50]	681	13–20	Sublingually	400	q3 h × 8	79.8%	12
			Vaginally	400	q3 h × 8	85.9%	12.3
Chaudhuri et al [51]	185	12–20	Vaginally	400	q6 h × 4	56.5% (<12 h)	12.59
			Vaginally	400	q12 h × 4	25.8% (<12 h)	16.41
Cheng et al [52]	16	12–25	Vaginally	200	q1 h × 12 h followed by 400 μg q1 h	81.3%	12

gestation) preferably using misoprostol tablets at 3-hourly intervals [53]. From Table 2, we can see that most of these studies use misoprostol with the time interval from 3 hours to 6 hours, and their result had a good abortion rate and short induction to abortion interval. It seems that 3–6 hours interval is a good choice for mid-trimester termination.

About the route of administration

Many studies investigated the different routes of administration of misoprostol, such as orally, vaginally, buccally, and sublingually [54], even with titrated oral misoprostol has been reported [55]. In 2000, Ngai et al [29] suggested that oral misoprostol is as effective as vaginal misoprostol if the dose was doubled. In the following year, a randomized trial of oral versus vaginal misoprostol was conducted by Gilbert and Reid [56] and suggested that the vaginal route of administration was significantly more effective. Cabrera et al [57] conducted a meta-analysis of published randomized controlled trials that compared sublingual and vaginal routes, and they said that sublingual and vaginal misoprostol are equally safe and effective for mid-trimester pregnancy termination. The 2011 Cochrane Database Systemic Review also recommended that the optimal route for administrating misoprostol is vaginally [53].

There are some factors that influence the induction-abortion interval. Dickinson and Doherty [58] published that nulliparity, younger maternal age, and increasing gestational age were associated with a longer induction-abortion interval, and the types of fetal anomaly had no impact on abortion duration. Dilek et al [59] studied the possible effect of cervical length on second-trimester pregnancy termination. They used a cutoff of 36 mm of cervical length by transvaginal measurement before administration of misoprostol and found that the length of cervix was not correlated with successful termination of pregnancy within 24 hours. Chou et al [60] told about the monitoring medical abortion with ultrasonogram and serum human chorionic gonadotropin.

From all the above studies and the list in Table 2, misoprostol, 400 μg given vaginally every 3–6 hours, is probably the optimal regimen for second-trimester abortion [4,61].

The scarred uterus

There were some case reports about uterine rupture in scarred uterus after the administration of misoprostol. Dickinson [62] published his results about scarred uterus. Misoprostol was used to induce abortion with 400 μg vaginally every 6 hours and the presence of a prior uterine scar did not impact on abortion duration. Thus he concluded that, in second-trimester abortion, the use of misoprostol in women with prior cesarean delivery was not associated with an excess of complications compared with women with unscarred uteri. Berghella et al [63] published their data about women with one prior low-transverse caesarean birth who underwent termination of pregnancy with misoprostol, the incidences of uterine rupture is 0.4%, the incidence of hysterectomy is 0%, and the incidence of transfusion is 0.2%. Fawzy and Abdel-Hady [64] used misoprostol 200 μg vaginally with 6 hours intervals on the 1st day and double the dose to 400 μg with the same intervals since the 2nd day in the women with three or more prior cesarean sections. This study had a 90.3% successful rate without any adverse outcome. However, for safety, it is recommended that women with a scarred uterus should receive lower doses of misoprostol and do not double the dose if there is no initial response [4].

The outcome of subsequent pregnancies

In 2009, Mirmilstein et al [65] reviewed the women who had undergone a misoprostol mid-trimester termination in their last pregnancy with those of a similar cohort of women without a history of use of misoprostol. It showed a possibility that termination of mid-trimester pregnancy with misoprostol increases the risk of preterm or very preterm delivery in a subsequent pregnancy. However, another case-control study was reported by Winer et al [66] in the same year, it included 245 cases and 490 controls and the result provided reassurance that induced abortion with misoprostol during the first or second trimester of pregnancy is safe for subsequent pregnancies. Larger studies are needed to confirm both of these results.

Adverse effects of misoprostol

Many adverse effects of misoprostol have been reported, include diarrhea, abdominal pain, headache, menstrual cramps, nausea and flatulence, chills, shivering, and fever, all of them are dose-dependent. The most common side effects are chills/shivering (38%), fever (35%), and diarrhea (24%). In pregnant women, chills, shivering, and fever are more commonly reported side effects [1]. Fever up to 40°C are associated with higher dose of misoprostol (e.g. 800 μg), shorter intervals, and oral or sublingual routes [5]. However, fever is transient and easily disappears after cooling and antipyretics. Diarrhea is another common adverse reaction, about 35% women were affected after the use of misoprostol [67]. Fortunately, it is mild and self-limited even without any management. As we know that the increased dosage was associated with a higher incidence of side effects, more than 800 μg of misoprostol was likely to have side effects, especially diarrhea [68]. Besides, fever was more common in the use of misoprostol by means of vaginal route.

Furthermore, misoprostol acid was found to be secreted in the colostrum within 1 hour after oral administration of 600 μg of misoprostol, thus we should avoid using misoprostol in nursing mothers because it may cause diarrhea in the baby [69].

Teratogenic effects of misoprostol

The package warned that misoprostol could cause birth defects if given to pregnant women. Teratogenic effects were reported with failed abortion and attempted to continue pregnancy after administration of misoprostol. Because this drug is listed as a pregnancy category X, the effects of fetus exposure to misoprostol *in utero* became highly concerned.

In 1993, the first report of seven infants whose mothers try to abort using misoprostol in the first trimester of pregnancy without success were born with limb defects and four of them had Möbius syndrome [70]. In the following literatures, the association of exposure of misoprostol during the first trimester of pregnancy and the occurrence of congenital abnormalities, such as skull defects, cranial nerve palsies, facial malformations, and limb defects had been reported. In 1998, Gonzalez et al [71] showed the distinctive phenotypes included equinovarus with cranial nerve defects, arthrogryposis of legs, and terminal transverse limb defects. They suggested that these congenital abnormalities were due to vascular disruption causing by the uterine contractions induced by misoprostol. Holmes [72] also concluded that the effect of vascular disruption caused by misoprostol may induce fetal limb defects. Another system review in 2006 showed that increased risks of congenital anomalies related to the use of misoprostol were found more significantly in Möbius sequence (congenital facial paralysis with or without limb defects) and terminal transverse limb defects than any other congenital defect [73]. However, the risk of fetal abnormality after the use of misoprostol is low, the estimated risk was less than 1% among those exposed fetus [74].

It is important for us to recognize these associated teratogenic effects and thorough consultation before prescribing this medication to patients regarding these risks, especially when failure of abortion occurs, is needed [75].

Conclusions

Multiple trials have proved that misoprostol is an effective agent for termination of second-trimester pregnancy. For termination of second-trimester pregnancy, using the combination of mifepristone and misoprostol seems to have the highest efficacy and shortest abortion time interval. When mifepristone is not available, misoprostol alone is a good alternative. Misoprostol, 400 μg given vaginally every 3–6 hours, is probably the optimal regimen for second-trimester abortion. More than 800 μg of misoprostol is likely to have more side effects, especially diarrhea.

Although, misoprostol can be used in women with scarred uterus for termination of second-trimester pregnancy, it is recommended that women with a scarred uterus should receive lower doses and do not double the dose if there is no initial response.

It is important for us to recognize the associated teratogenic effects of misoprostol and thorough consultation before prescribing this medication to patients is needed.

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